BMJ Open

Oral Janus kinase inhibitors and venous thromboembolic events in atopic dermatitis: protocols for a case–time control study and a nested case-control study based on the French national health insurance (SNDS) cohort

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To cite: Berthe P, Scailteux L-M, Lescoat A, *et al*. Oral Janus kinase inhibitors and venous thromboembolic events in atopic dermatitis: protocols for a case–time control study and a nested case-control study based on the French national health insurance (SNDS) cohort. *BMJ Open* 2022;**12**:e059979. doi:10.1136/bmjopen-2021-059979

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-059979).

Received 11 December 2021
Accepted 23 July 2022

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ABSTRACT

Introduction Atopic dermatitis (AD) is a highly prevalent, chronic, inflammatory skin disease. Several orally administered Janus kinase inhibitors (JAKis, including baricitinib, upadacitinib and abrocitinib) have received a marketing authorisation for AD.

Clinical trials in rheumatoid arthritis (RA) have flagged up a potential risk of JAKi-induced venous thromboembolic events (VTEs). Accordingly, the summary of product characteristics for a JAKi must mention VTEs as potential adverse drug reactions. In contrast to RA, AD per se is not associated with an elevated risk of VTEs. Assessing this potential risk among patients with AD would shed further light on the putative underlying relationship between JAKis and VTEs.

Our research question is to investigate whether JAKi administration increases the risk of VTEs in adults with AD. Our primary objective is to assess the risk of VTEs in adults with AD exposed to JAKis compared to AD adults not exposed to JAKis, and our secondary objective is to evaluate whether JAKi initiation acts as a trigger of VTEs in adults with AD within 3 months.

Methods and analysis Hence, we have designed (1) a nested case–control study and (2) a case–time control study in a cohort of adults with AD with data from the French national health insurance system (2017–2025). Here, we describe the study protocol, our methodological choices and certain novel aspects, including the combined value of the two assumptions and the use of an exhaustive national health insurance database with potentially greater statistical power for studying rare events in the population of patients with AD at a low risk of VTEs (thus limiting the influence of confounding factors).

Ethics and dissemination The protocol has been approved by an independent ethics committee and registered with the French National Data Protection Commission. The study's findings will be published in peer-reviewed scientific journals and presented at international conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A population-based study using the exhaustive French national health insurance database would provide additional insight into the risk of venous thromboembolic events (VTEs). Advantageously, this nationwide study should be able to exhaustively identify VTEs, the time of their occurrence, and prescriptions of JAK inhibitors.

⇒ By studying atopic dermatitis (AD), we hope to avoid a major source of confounding bias; in contrast to rheumatoid arthritis, AD is not associated per se with an elevated risk of VTEs.

⇒ The limitations of this study protocol (based on the use of French national health insurance database) include a lack of data on certain risk factors for VTEs (including obesity and a family history of thromboembolic disease)

⇒ A potential lack of statistical power.

INTRODUCTION

Atopic dermatitis (AD) is a highly prevalent, pruritic, inflammatory disease skin that occurs in both adults (3%–10%)[1–3] and children (15%–20%).[1 4 5] Approximately 2%–8% of adults with AD have severe forms; the associated impairments in quality of life make AD a disabling disease. Severe AD is frequently associated with other atopic comorbidities (eg, asthma, allergic rhinitis, allergic conjunctivitis and food allergy) and may be associated with psychiatric disorders.

The European guidelines on the management of AD in adults recommend first-line treatment with topical anti-inflammatory drugs (topical corticosteroids and tacrolimus) and then (if the treatment fails) systemic immunosuppressants.[6 7] In late 2017,

the management of treatment-refractory AD was revolutionised by the marketing of the first biological drug, dupilumab (a subcutaneously administered monoclonal antibody against interleukin (IL)-4 and IL-13 receptors).[8 9] Other systemic treatments have since received (or are awaiting) marketing authorisation: baricitinib (an orally administered Janus kinase (Jak) 1 and 2 inhibitor (Janus kinase inhibitor (JAKi)),[10–13] upadacitinib (an orally administered JAK1 inhibitor),[14–16] abrocitinib (another orally administered JAK1 inhibitor)[17–19] and tralokinumab (a subcutaneously administered anti-IL-13 monoclonal antibody).[20 21]

JAKis constitute a new family of orally administered molecules that target the JAK signal transducer and activator of transcription (STAT) pathway. Jaks are involved in the transduction of intracellular signals in response to various cytokines and growth factors involved in haematopoiesis, inflammation and immune functions.

In the European Union, baricitinib was approved for the treatment of active, moderate-to-severe rheumatoid arthritis (RA) in adults in 2017 and for moderate-to-severe AD in adults who are candidates for systemic drug treatment in 2021. Upadacitinib was approved for the treatment of adults with moderate-to-severe active RA, psoriatic arthritis (PsA) or ankylosing spondylitis (AS) in 2020 and 2021 and for the treatment of moderate-to-severe AD in adults and adolescents (aged 12 or over) who are candidates for systemic drug treatment in August 2021. Lastly, abrocitinib was approved very recently by the European Medicines Agency (EMA) for the systemic treatment of moderate-to-severe AD in adults and adolescents.

Clinical trials in RA have flagged up a potential risk of JAKi-induced venous thromboembolic events (VTEs, including deep vein thrombosis and pulmonary embolism).[22–26] Although the EMA approved low (2 mg) and high (4 mg) doses of baricitinib, the Food and Drug Administration approved only the 2 mg dose because of the VTE risk. On a broader scale, the summary of product characteristics for a JAKi must mention VTEs as potential adverse drug reactions. The safety profiles of baricitinib and upadacitinib in patients with RA have been described in nine and five clinical studies, respectively. The estimated incidence of VTEs ranged from 0.3 to 0.6 per 100 person-years.[22 27]

Due to the presence of systemic inflammation, RA per se can induce thromboembolic events, and the treatment of RA with anti-inflammatory drugs helps to reduce the cardiovascular and thromboembolic risks.[25 28] Furthermore, most patients with RA are aged over 50 at diagnosis and have higher prevalence of obesity and a higher incidence of VTEs. In this case, the interplay between RA, JAKis and thromboembolic risk is particularly difficult to characterise.

The pathogenic links between JAKis and a potentially greater risk of thromboembolic disease are poorly understood, and the literature data are contradictory. The potential thromboembolic risk might be related to an imbalance between prothrombotic and antithrombotic signals, including the inhibition of proinflammatory signals (such as interferon-dependant pathways) and the paradoxical inhibition of JAK–STAT-dependent anti-inflammatory pathways (such as the IL-10 pathway that helps to limit clot formation under normal conditions).[29 30] JAKis that influence JAK2-dependent signalling (such as baricitinib) might also promote platelet formation from megakaryocytes, as evidenced by a transient increase in the platelet count following JAKi initiation. Nonetheless, a causal link between transient thrombocytosis and VTE has never been proven.[22]

The results of meta-analyses of the links between JAKis and the risk of thromboembolic and/or cardiovascular events are summarised in table 1.[31–37]

Most of the meta-analysed data came from clinical trials rather than real-life studies with a longer follow-up period. The meta-analyses concluded that although the JAKi treatment is associated with an elevated risk of VTEs, the association is not statistically significance. Lastly, the meta-analyses did not encompass data on VTEs treated in primary care facilities (ie, on an outpatient basis). Two analyses of US medical–administrative databases did not find a difference in the VTE risk between patients with RA taking tofacitinib and those taking an antitumour necrosis factor agent (HR=1.13 (95% CI 0.77 to 1.65) and HR=1.33 (95% CI 0.78 to 2.24), respectively).[38 39] However, the researchers could not rule out such a risk and only considered VTEs leading to hospital admission.[38 39]

A population-based study of a health insurance database (the *Système National des Données de Santé* (SNDS)) would provide additional insights by focusing on the VTE risk. The advantages of studying a health insurance database include the precise, national-level identification of JAKi prescriptions, VTEs and the time of occurrence (eg, relative to treatment initiation). Furthermore, studying AD avoids a major source of confounding bias; in contrast to RA and inflammatory bowel disease, AD is not associated with an increased risk of VTE[40] and predominantly affects a younger population with a lower prevalence of concomitant cardiovascular comorbidities or obesity.

Here, we describe the protocol for the 'JAK inhibitors and ThromboEmbolic Risk' study of the association between JAKis and VTEs in AD using real-world evidence from an exhaustive French medical–administrative database. We also discuss our methodological choices. Our primary objective is to assess the risk of VTEs in adults with AD exposed to JAKis compared with AD adults not exposed to JAKis, and our secondary objective is to evaluate whether JAKi initiation acts as a trigger of VTEs in adults with AD within 3 months, corresponding to two different methodological approaches.

METHODS AND ANALYSIS

Overall study design

The literature data on the temporal relationship between the initiation of treatment with a JAKi and the

Table 1 List of meta-analyses on the risk of VTEs during treatment with JAKis

First author	Date of publication	JAK inhibitor	Indication	Studies included (n)	Type of studies included	Patients included (n)	Median follow-up (weeks)	Events among exposed participants (n)	Events among non-exposed participants (n)	Results OR (95% CI)	Methods used
Xie *et al*[31]	2019	Tofacitinib, baricitinib, upadacitinib, peficitinib, decernotinib	RA	26	RCT	11 799	Placebo-controlled period: 12 Dose-comparison period: 24	12	3	All JAKis: 1.16 (0.48 to 2.81) Tofacitinib: 0.17 (0.03 to 1.05) Baricitinib: 2.33 (0.62 to 8.75) Upadacitinib: 1.77 (0.20 to 16.00)	Mantel-Haenszel fixed-effect method
Xie *et al*[32]	2019	Tofacitinib	RA, PsA, CPP, UC, CD, AS	27	RCT	13 611	Placebo-controlled period: 12 Dose-comparison period: 24	1	5	0.03 (0.00 to 0.21)	Peto method
Olivera *et al*[33]	2020	Tofacitinib, upadacitinib, filgotinib, baricitinib	RA, AS, UC, CD, CPP	10	RCT Cohorts	5143	26	12	3	All JAKis: 0.90 (0.32 to 2.54)	Random-effect model
Giménez Poderós *et al*[34]	2020	Tofacitinib, baricitinib	RA, KT, UC, CPP, CD, PsA, AD, DKD, SLE, JIA, SS	59	RCT Cohorts	25 947	16	24	23	Tofacitinib: 0.29 (0.10 to 0.84) Baricitinib: 3.39 (0.82 to 14.04)	Fixed-effect or random-effect model, with application of the most conservative model in each case
Yates *et al*[35]	2020	Tofacitinib, baricitinib, upadacitinib, filgotinib	RA, PsA, AS, UC, CD, CPP	42	RCT	17 269	Unavailable	15	4	All JAKis: 0.68 (0.36 to 1.29)	Mantel-Haenszel fixed-effect method
Wang *et al*[36]	2020	Upadacitinib	RA	3	RCT	2852	Unavailable	3	1	2.34 (0.15 to 15.02)	Random-effect model
Bilal *et al*[37]	2021	Abrocitinib, baricitinib, decernotinib, filgotinib, peficitinib, ruxolitinib, tofacitinib	RA, AD, SLE, CPP, AS, PsA, UC, pancreatic cancer, breast cancer	29	RCT	13 910	48	50	27	All JAKis: 0.91 (0.57 to 1.47) Baricitinib: 1.12 (0.27 to 4.69) Decernotinib: 1.07 (0.18 to 6.43) Filgotinib: 2.13 (0.22 to 20.64) Ruxolitinib: (0.31 to 2.29) Upadacitinib: 2.25 (0.55 to 9.25) Tofacitinib: 0.27 (0.08 to 0.89)	Random-effects model

AD, atopic dermatitis; AS, ankylosing spondylarthritis; CD, Crohn's disease; CPP, chronic plaque psoriasis; DKD, diabetic kidney disease; IR, incidence rate; JAKi, Janus kinase inhibitor; JIA, juvenile idiopathic arthritis; KT, kidney transplantation; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomised clinical trial; SLE, systemic lupus erythematosus; SS, systemic sclerosis; UC, ulcerative colitis; VTE, venous thromboembolic event.

occurrence of a VTE are contradictory. Some studies suggest that the incidence rates of VTEs are consistent over time,[22] whereas other indicate that the incidence rates are clustered soon after the start of exposure.[41] The study null hypotheses are formulated as follows: (1) VTE risk is equal in adults with AD exposed or not exposed to JAKis; and (2) JAKi initiation does not trigger VTE. We will therefore use two different methodological approaches to investigate the VTEs and the JAKis prescribed for AD: (1) a nested case–control study in a cohort of adults with AD (analysis 1) and (2) a case–time control study (analysis 2).

The overall study design is summarised in figure 1.

Place and study time

The analysis period will run from January first, 2017, to August 31st, 2025, in France.

Data sources

We will analyse the French national health insurance database (SNDS), which covers 98% of the 66 million people in France. The SNDS database contains anonymous data on individuals' demographic characteristics (sex, dates of birth and (if applicable) date of death); all healthcare reimbursements, including drugs (with the prescription filling date, the prescriber's medical specialty, laboratory tests, outpatient care/visits, all hospital stays, and the associated diagnoses (coded according to the International Classification of Diseases, 10th Revision (ICD-10), all causes of death (classified according to the ICD-10 codes) and the attribution or not of 'chronic disease' status ('affection de longue durée' (ALD), giving entitlement to the full coverage of related healthcare costs and again coded according to ICD-10 codes). Information on medical procedures or biological results are not available in the SNDS.

Selection criteria and constitution of the target cohort

To avoid indication bias and form a homogeneous group of patients in terms of medical care, we will build up a cohort of adults with AD and who start systemic immunomodulatory treatment for this disease.

In France, AD is a chronic condition that is mostly managed in outpatient settings and not during hospital stays. Furthermore, AD does not give entitlement to ALD chronic disease status. All eligible adults (aged 18 or over) with a priori AD will be identified as follows:

- Adults (aged 18 or over) with an initial fulfilment of a prescription for dupilumab, cyclosporine, methotrexate, tralokinumab or a JAKi (baricitinib, upadacitinib or abrocitinib), two or more fulfilments of topical corticosteroids, and a consultation with a dermatologist between 1 January 2017 and 31 December 2024.
- Adults with no fulfilments of dupilumab, cyclosporine, methotrexate, tralokinumab or JAKi (baricitinib, upadacitinib or abrocitinib) prescriptions in the year prior to cohort entry.
- Adults with no other indications for dupilumab, cyclosporine, methotrexate, tralokinumab or the JAKis baricitinib, upadacitinib or abrocitinib (ie, RA, PsA, AS, ulcerative colitis, lupus, organ or bone marrow transplant, nephrotic syndrome and psoriasis) identified through 'ALD' chronic disease status or the hospital discharge ICD-10 codes, between 1 January 2016 and 31 December 2024.
- Adults with follow-up starting on the date of the first filled prescription of a JAKi (baricitinib, upadacitinib or abrocitinib), dupilumab, tralokinumab, cyclosporine or methotrexate, up to 31 August 2025.

Outcomes

The primary endpoint is VTE; it is a composite endpoint encompassing pulmonary embolism, managed mostly in hospital and identified through hospital discharge ICD-10 code (table 2) and deep vein thrombosis managed mostly in an outpatient setting and identified through a dedicated and validated algorithm (manuscript under review). The cases will be adults with AD and incident deep vein thrombosis or pulmonary embolism, managed in an outpatient setting, a hospital or an emergency department.

The index date is the date of the VTE.

To study cases of 'unprovoked' VTEs, we will exclude the following cases of adults with 'provoked' VTEs[42]:

- Initiation of oral oestroprogestative contraception in the 3 months before the index date.
- Pregnancy (including a 2-month postpartum period) before the index date.
- Surgery (orthopaedic surgery involving long bones or the pelvis, or other major surgery) in the 4 weeks before the index date.
- Prolonged hospitalisation (>72 hours) in the 4 weeks before the index date.
- A diagnosis of cancer (including haematological malignancies but not including non-melanoma skin cancer) before the index date.
- Fulfilment of one or more prescriptions for preventive or curative treatments with anticoagulants, including heparins, antivitamin K agents and direct oral anticoagulant (ensuring the exclusion of patients with a history of VTEs and persistent risk factors for VTE recurrence) before the index date (for VTEs managed in hospital or in an emergency department) or before the index date minus 7 days (for adults starting an anticoagulant treatment before hospitalisation for VTE).

Data analysis

The characteristics of the JAKis-treated population of patients with AD will be described, together with the time interval between JAKi initiation and the occurrence of the VTE. We will explore the risk function and the potential time-varying association.

- Nested case-control study (analysis #1)
- Nested case-time-control study (analysis #2): in patients with a VTE, we shall compare the frequency of JAKi initiation in the risk period (before VTE) with the frequency of JAKi initiation in the reference period (prior to the risk period).

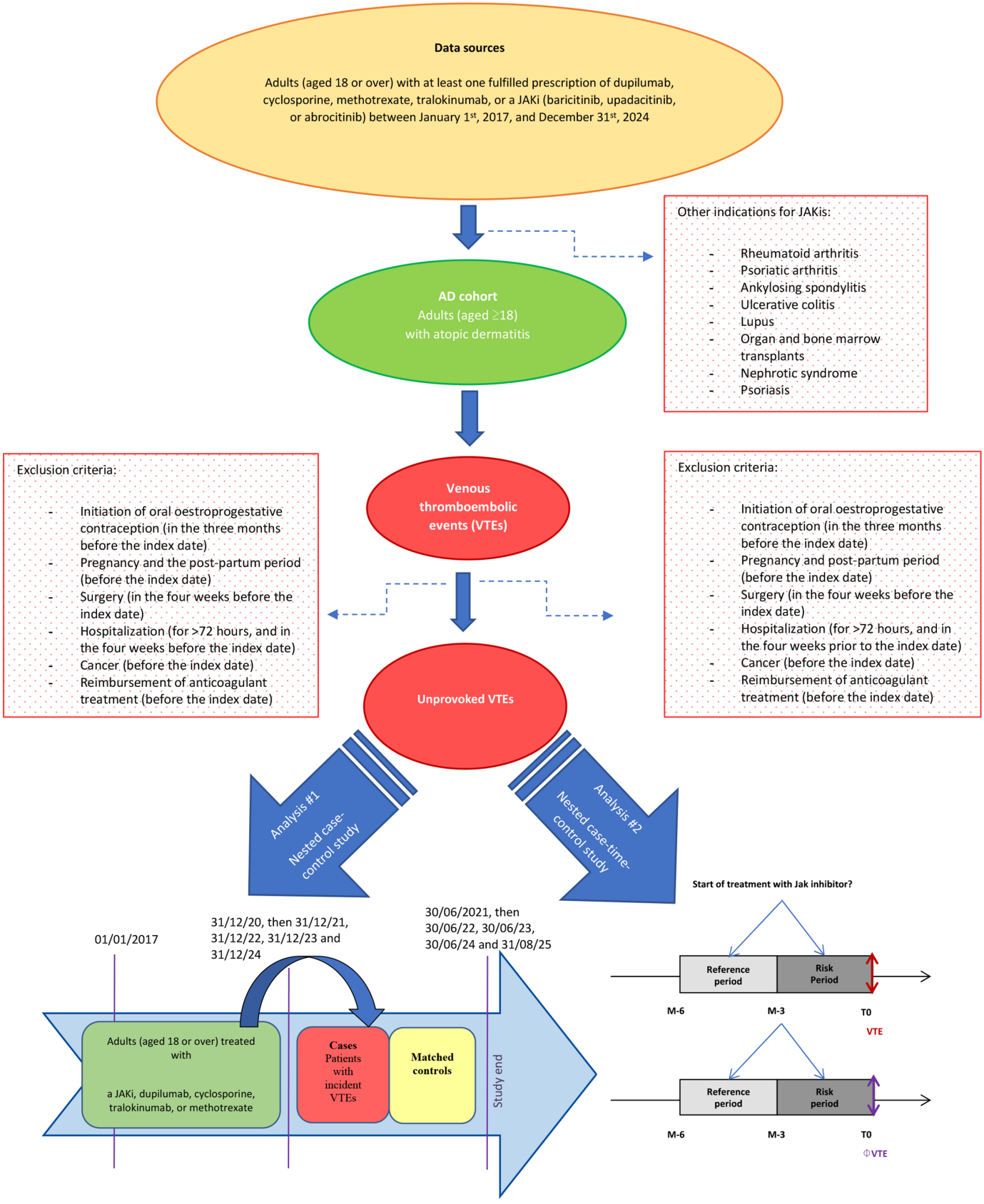

Figure 1 Overall study design. AD, atopic dermatitis; JAKi, Janus kinase inhibitor.

Table 2 List of variables

Variables	Registry	Code
AD		
AD	PMSI	ICD-10 code L20
Topical corticosteroids	DCIR	ATC codes D07AB01, D07AB02, D07AB03, D07AB04, D07AB05, D07AB06, D07AB07, D07AB08, D07AB09, D07AB10, D07AB11, D07AB19, D07AB21, D07AB30, D07AC01, D07AC02, D07AC03, D07AC04, D07AC05, D07AC06, D07AC07, D07AC08, D07AC09, D07AC10, D07AC11, D07AC12, D07AC13, D07AC14, D07AC15, D07AC16,D07AC17, D07AC18, D07AC19, D07AC20, D07AC21, D07AD01, D07AD02
Consultation with a dermatologist	DCIR	PFS_SPE_COD or PFE_SPE_COD code 05
Exposure		
Baricitinib	DCIR	ATC code L04AA37
Upadacitinib	DCIR	ATC code L04AA44
Abrocitinib	DCIR	ATC code D11AH08
Dupilumab	DCIR	ATC code D11AH05
Tralokinumab	DCIR	ATC code D11AH07
Cyclosporine	DCIR	ATC code L04AD01
Methotrexate	DCIR	ATC code L01BA01
VTEs		
VTEs	PMSI, DCIR	EPIGETBAM algorithm under submission
Exclusion criteria		
Oral oestroprogestative	DCIR	ATC codes G03AA01, G03AA02, G03AA03, G03AA04, G03AA05, G03AA06, G03AA07, G03AA08, G03AA09, G03AA10, G03AA11, G03AA12, G03AA13, G03AA14, G03AA15, G03AA16, G03AB01, G03AB02, G03AB03, G03AB04, G03AB05, G03AB06, G03AB07, G03AB08
Pregnancy	PMSI	ICD-10 code Z321
Hospital stay >72 hours, with or without surgery	PMSI	ICD-10 codes
Cancer and haematological malignancies	PMSI	ICD-10 codes C00 to C43 and C45 to C97, D00 to D03, D05 to D09, D37 to D48, or ALD n°30
Anticoagulant treatment	DCIR	ATC codes B01AA01, B01AA02, B01AA03, B01AA04, B01AA07, B01AA08, B01AA09, B01AA10, B01AA11, B01AA12, B01AB01, B01AB02, B01AB04, B01AB05, B01AB06, B01AB07, B01AB08, B01AB09, B01AB10, B01AB11, B01AB12, B01AB51, B01AE01, B01AE02, B01AE03, B01AE04, B01AE05, B01AE06, B01AE07, B01AF01, B01AF02, B01AF03, B01A×01, B01A×04, B01A×05
Rheumatoid arthritis	PMSI DCIR	ICD-10 codes M069, M0690, M0691, M0692, M0693, M0694, M0695, M0696, M0697, M0698, M0699, M06 or ALD n°22
Psoriatic arthritis	PMSI DCIR	ICD-10 codes M0700, M0701, M0702, M0703, M0704, M0705, M0706, M0707, M0708, M0709, M072, M0720, M0721, M0722, M0723, M0724, M0725, M0726, M0727, M0728, M0729, M073, M0730, M0734, M0732, M0733, M0734, M0735, M0736, M0737, M0738, M0739
Ulcerative colitis	PMSI DCIR	ICD-10 codes K519 or ALD n°24
Lupus	PMSI DCIR	ICD-10 codes L93, M32 or ALD n°21
Organ and bone marrow transplants	PMSI DCIR	ICD-10 codes Z940, Z941, Z942, Z943, Z944, Z945, Z946, Z947, Z948, Z9480, Z94800, Z94801, Z9481, Z9482, Z94802, Z94803, Z94804, Z94809, Z949
Nephrotic syndrome	PMSI DCIR	ICD-10 code N04 or ALD n°19

Continued

Table 2 Continued

Variables	Registry	Code
Psoriasis	PMSI DCIR	ICD-10 code L40, L400, L401, L402, L403, L404, L405, L408, L409
Ankylosing spondylitis	PMSI	ICD-10 codes M45, M450, M451, M452, M453, M454, M455, M456, M457, M458, M459 or ALD n°27
Covariates		
Charlson Comorbidity Index	PMSI	Algorithm developed by Bannay *et al*.[47]
Systemic corticosteroids	DCIR	ATC codes H02A and H02B
Asthma	PMSI DCIR	ICD-10 codes J45, J450, J451, J458, J459, J46 ATC code R03
Statins	DCIR	ATC codes C10AA, C10B

ALD long-term chronic disease status giving entitlement to full coverage of related healthcare costs.
AD, atopic dermatitis; ALD, Affection Longue Durée; ATC, Anatomical Therapeutic Chemical; DCIR, Données de Consommation Inter Régimes; ICD-10, International Classification of Diseases 10th Revision; PMSI, Programme de Médicalisation des Systèmes d'Information; VTE, venous thromboembolic event.

Analysis 1: a nested case–control study of a cohort of adults with AD

The association between exposure to JAKis and the occurrence of VTEs will be investigated in a nested case–control study of a cohort of adults with AD requiring systemic treatment.

Adults with AD will be considered to have been exposed to JAKis if they have at least one fulfilled prescription for a JAKi prior to the index date. Adults with AD will be assigned to a 'JAKi user' category or a 'JAKi never-user' category, based on the prior fulfilment closest to the index date. Subgroups of JAKi users will be defined as follows: for current JAKis users, the last prescription will have been fulfilled in the month before the index date: for recent JAKis users, the last prescription will have been fulfilled between 1 and 4 months before the index date; and for past JAKis users, the last prescription will have been fulfilled more than 4 months before the index date. Furthermore, for current JAKi users; the number of JAKi prescription fulfilments and the total cumulative dose of JAKis received before the index date will be calculated.

References will be adults with AD whose most recent prescription fulfilment before the index date (regardless of how long before) will have been for another systemic treatment for AD.

For each case (adults with AD having experienced a VTE), four controls will be selected from the target AD cohort. Controls must not have experienced a VTE at the time of their selection. Cases and controls will be matched for age, sex and length of exposure at the case's index date. The inclusion and exclusion criteria applied to cases will be applied to the matched controls. It will be possible for a control to become a case after his/her selection (density sampling).[43] We will estimate ORs using conditional logistic regression. We will consider systemic treatment of AD as a binary variable: JAKi users (baricitinib, upadacitinib or abrocitinib) versus users of other systemic drugs (dupilumab, tralokinumab, cyclosporine or methotrexate). We will consider drug exposure as a continuous variable. The primary analysis will compare current JAKi users with JAKi never-users. The secondary analyses will cover 'recent JAKi user' status, 'past JAKi user' status and use of each individual JAKi (baricitinib, upadacitinib and abrocitinib). A Schneeweiss diagram for analysis 1 is shown in figure 2.[44]

Analysis 2: a case-only design – a nested case–time control study of a cohort of adults with AD

To evaluate whether or not initiation of a JAKi increases the risk of VTE in the following 3 months (ie, a 'triggering effect'), we will perform a case–time control analysis.

In the field of pharmacoepidemiology, case–time control studies can be used to study an acute, early-onset adverse event during treatment.[45] A VTE is sudden (with a short time interval between the pathophysiological cause and the clinical manifestations) and is easy to date by screening for specific treatments and additional investigations (including Doppler ultrasound). The majority of the VTEs observed in clinical trials[22] or reported in pharmacovigilance databases[41] occurred within 3–4 months of JAKi initiation.[46] Furthermore, the case-only design can control for potential confounding factors (such as obesity and physical activity) not recorded in the French health insurance database.

Only patients with AD exposed to a JAKi and having experienced a VTE (ie, cases) will be analysed. The case–time control design compares the exposure status immediately before the event (the risk period) with exposure during a designated (earlier) reference period. Each VTE case will serve as his/her own control during a comparison of the risk period (0–3 months before occurrence of the VTE) with the reference period (3–6 months before occurrence of the VTE). Each VTE case will be assessed for exposure (yes/no) during the risk period and during the reference period. Only participants whose status differs

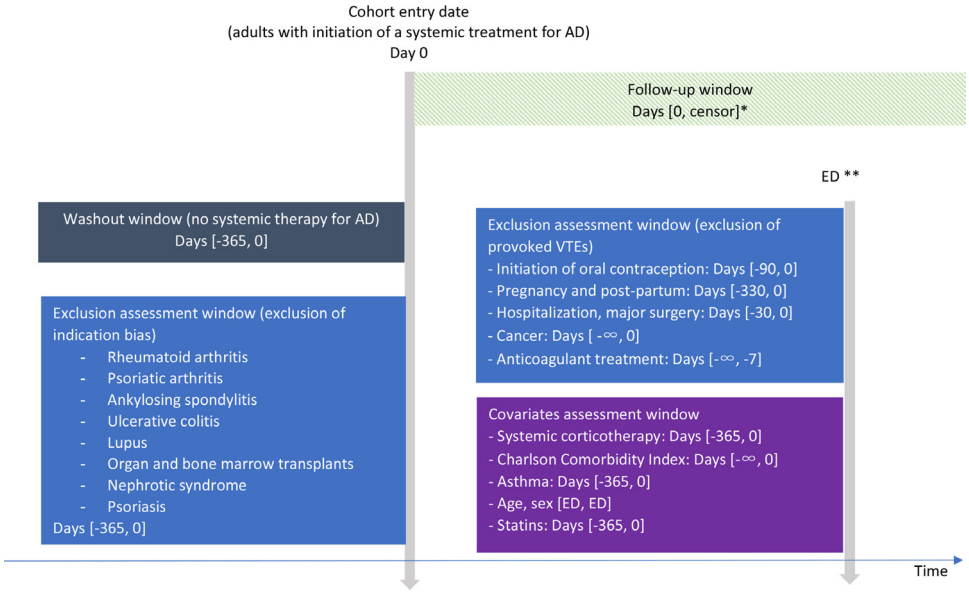

Figure 2 Schneeweiss diagram for analysis #1 (44). *Censored at the date of the first VTE, death, emigration or the end of the study period. **ED denotes the date of the first VTE (the index date). AD, atopic dermatitis; ED, event date; VTE, venous thromboembolic event.

when comparing the two periods (ie, discordants) will be considered in our estimation of the OR. To take account of the expected increase in JAKi prescription, the case–time control analysis will include a selection of controls matched with VTE cases. Each VTE case will be matched for age and sex with five controls without VTEs and who will be randomly selected from the AD target cohort. The date of the VTE will be used as the index date for the matched controls. The aforementioned defined risk and reference periods will be screened for JAKi initiation among the controls in the same way as among the cases, and a case-crossover OR for controls will be computed. The case–time control OR (95% CI) will be estimated with a conditional logistic model by considering the interaction term between the exposure of interest (JAKi initiation) and the participant's status (case or control). The case–time control OR will correspond to the ratio between the respective case-crossover ORs obtained in cases and controls.

Sensitivity analyses in which the durations of the risk and reference period are modified will be performed as follows: the risk period will be defined as 0–2 months or 0–4 months before the VTE, and the control period will be defined as 2–4 months or 4–8 months before the VTE. Furthermore, sensitivity analysis will be performed for analyses 1 and 2 by changing the patient selection criteria and excluding patients with asthma. Lastly, we shall exclude patients having initiated oral oestroprogestative contraception in the 6 or 12 months before the date of the VTE in cases or the corresponding date in controls.

Covariates

We used a directed acyclic graph (figure 3) to describe covariates, mediators and potential confounding factors in the relationship between JAKis and VTEs.

The results will be adjusted for several covariates, including the patient's chronic comorbidities (using Bannay *et al*'s algorithm for use of the Charlson Comorbidity Index with an electronic healthcare database[47 48]) and the use of statins[49] or systemic corticosteroids.[50] Obesity is either not documented or only partially documented in the SNDS database; in Europe, most adults with AD are not obese.[51] The case-only design approach (analysis 2) avoids this potential confounding factor, since the patient is his/her own control. The SNDS database does not contain identifiable information on a family history of venous thromboembolic disease.

Asthma (the most important atopic comorbidity in AD) will be assessed and defined as follows: an ICD-10 code J45–J46 and/or at least two fulfilments of a drug for the treatment of obstructive airway diseases (an Anatomical Therapeutic Chemical code of R03). The study variables are listed in table 2.

Sample size

Based on a frequency of exposure to JAKi among the targeted cohort of 25%, a 1:4 case:control ratio, and a statistical significance threshold of 0.05, the sample sizes required for a power of 80% in a comparison of JAKi exposure in cases versus controls are as follows: 1836 participants (306 cases and 1530 controls) for detecting an OR of 1.5, 618 participants (103 cases and 515 controls) for detecting an OR of 2, 354 participants (59 cases and 295 controls) for detecting an OR of 2.5, 246

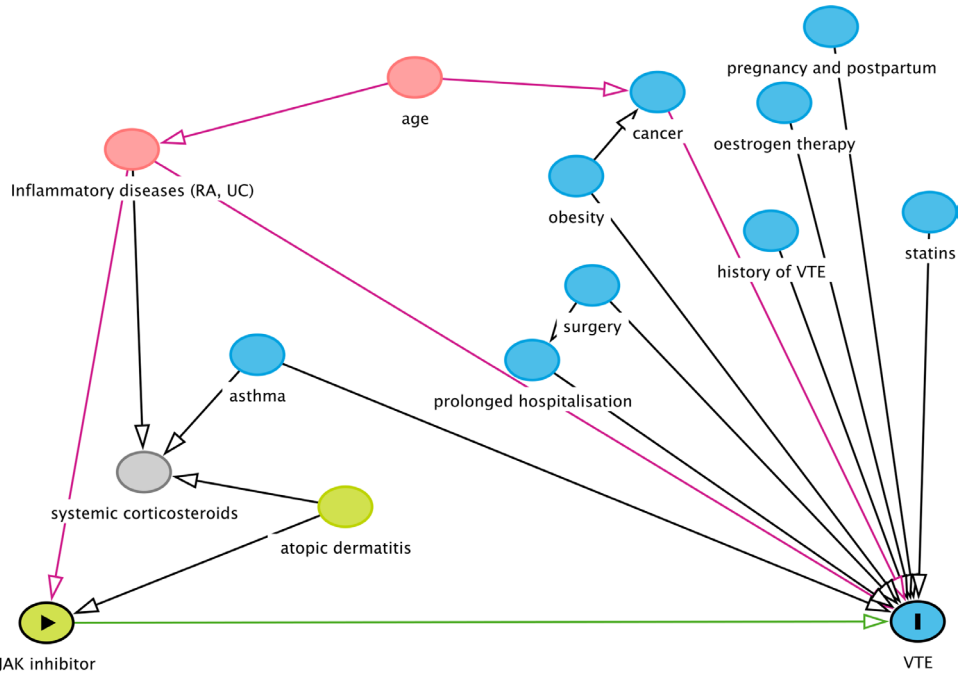

Figure 3 A directed acyclic graph of the relationship between JAKis, AD and VTEs. AD, atopic dermatitis; JAKi, Janus kinase inhibitor; RA, rheumatoid arthritis; UC, ulcerative colitis; VTE, venous thromboembolic event.

participants (41 cases and 205 controls) for detecting an OR of 3 and 192 participants (32 cases and 160 controls) for detecting an OR of 3.5. These calculations do not take account of matching, which will tend to increase the power in an unknown manner. The estimated power calculation is given in table 3. A final power calculation will be performed at the end of the study.

The estimated incidence of thromboembolic diseases in France is one per 1000 per year; approximately 50 000 adults with a follow-up of 3 years are required. The target population for baricitinib/upadacitinib has been estimated between 26 500 and 42 500 by the French High Authority for Health[52]; this is almost certainly an underestimate, given that courses of treatment with cyclosporine are short.

Patient and public involvement

A patient will join the independent scientific committee and will participate in the discussion of the results. This patient is the director of the French Eczema Association (https://www.associationeczema.fr/). Once the study will be published, patients with AD who are members of the association will be informed of the results in the form of newsletter suitable for a non-specialist audience through the website of the association.

ETHICS AND DISSEMINATION

In accordance with French legislation, the protocol has been approved by an independent ethics committee (*Comité éthique et scientifique pour les recherches, les études et*

Table 3 Power calculation for analysis 1

Frequency of exposure to JAKis in the targeted cohort	OR	Nominal power	Controls (n)	Cases (n)	Participants (total n)
0.50	1.5	0.8	1275	255	1530
0.50	2.0	0.8	465	93	558
0.50	3.0	0.8	205	41	246
0.25	1.5	0.8	1530	306	1836
0.25	2.0	0.8	515	103	618
0.25	2.5	0.8	295	59	354
0.25	3.0	0.8	205	41	246
0.25	3.5	0.8	160	32	192

JAKi, Janus kinase inhibitor.

les évaluations dans le domaine de la santé, Paris, France; reference: 4523600, dated 17 June 2021) and has been registered with the French National Data Protection Commission (*Commission Nationale de l'Informatique et des Libertés*, Paris, France; reference: 921265, dated 28 June 2021). The study's findings will be published in peer-reviewed scientific journals and presented at international conferences.

The data will be consulted via the French national health insurance system's (*Caisse Nationale de l'Assurance Maladie*) portal; the investigators' access is restricted to the scope of the study. The data were not extracted from the main database but were analysed in a dedicated project area on the server. The investigators will comply with the reference framework applicable to the SNDS database (as set out in the government act dated 22 March 2017).

The study protocol has been registered at France's Health Data Hub (www.health-data-hub.fr). The statistical analysis plan and data management book will now be drafted. The first results are expected in late 2025. The study's findings will be published in peer-reviewed scientific journals and presented at international conferences.

DISCUSSION

A population-based study of a cohort of adults with AD documented in the SNDS French national health insurance database should provide additional insights on the potential association between VTE and JAKis (baricitinib, upadacitinib and abrocitinib).

There are several possible pathophysiological explanations for an elevated risk of VTE during treatment with a JAKi. First, the leading hypothesis states that the thrombogenic effect is related to the thrombocytosis associated with baricitinib use.[22] However, a clear time-domain or quantitative association between the platelet count and the occurrence of VTE has not been observed.[22] Furthermore, elevation of the platelet count is not observed in people treated with other JAKis, including upadacitinib.[53] Second, the JAK two pathway has an important role in haematopoiesis and might promote VTE. Paradoxically, inhibition of the JAK2 pathway by JAKis does not account for the occurrence of VTE: in Vaquez disease and essential thrombocythemia, an activating mutation in JAK 2 increases the risk of arterial and venous thrombotic events.[54] Data from mouse models suggest that JAK V617F expression induces hypersensitivity to fibrinogen, thrombopoietin and other endogenous prothrombogenic factors.[55]

The literature data on the potential risk are contradictory and do not enable a firm conclusion about the association between JAKis and VTE to be drawn. A false association might result from methodological bias. For example, selection bias occurs when including patients who have received several courses of systemic treatment (and so might have more severe disease and a higher thromboembolic risk) are included in clinical trials (especially in open-label trials in RA).[22 24] Confounding bias may occur because the disease treated with JAKi is itself associated with a higher risk of VTE; this is particularly true for RA. Indeed, the thromboembolic risk is known to be two to three times higher in patients with RA[25] than in the general population.[28 56] The baseline risk also appears to be elevated other systemic inflammatory diseases, including inflammatory bowel disease.[57 58] In contrast, adults managed for moderate-to-severe AD are not known to have an elevated thromboembolic risk and are also younger than patients with RA; hence, the baseline risk of VTEs is lower. Published data on this indication are scarce: the only two meta-analyses included data from four randomised clinical trials evaluating the efficacy of baricitinib and abrocitinib in AD.[34] The lack of a significant association might have several explanations: (1) a lack of power would apply if the number of JAKi-exposed patients experiencing a VTE is low; meta-analyses have provided inconclusive results due to the rarity of the event and the predominant inclusion of clinical trial data; (2) insufficient follow-up in clinical trials (given the latency between JAKi initiation and VTE occurrence); and (3) a lack of specific detection of VTEs (requiring a targeted initial assessment and follow-up and perhaps a longer follow-up period). Lastly, it is unclear whether the published studies considered only VTEs leading to a hospitalisation or, in contrast, all VTEs. In France, the majority of VTEs are managed in an outpatient setting.[59]

Our implementation of two complementary methodological approaches should shed more light on this question. The case–control study is carried out on a population of patients with AD with similar disease severity levels and receiving similar intensities of systemic treatment. This design assumes that after initiation of a JAKi, the risk of a VTE is constant. The case–time control design will be applied to address (1) the assumption whereby a JAKi triggers a VTE and (2 the issue of residual confounding factors. This study design is particularly suitable when the outcome is sudden and easily dated, as is the case here.[60–62] The hypothetical triggering effect is based on (1) the transient thrombocytosis observed with baricitinib early after treatment initiation[63 64]; (2) pharmacovigilance data from France and North America,[41 46] where more than half of the reported VTEs occurred within 120 days of JAKi initiation[46]; and (3) the fact that other drugs (such as contraceptives) can trigger VTEs.[65–69] An increase over the study period in the prevalence of JAKi use for AD is expected; the case–time control design considers time trends in the prevalence of exposure that might introduce a confounding effect in a case-crossover design. We chose to study unprovoked VTEs by excluding well-known risk factors for thromboembolic disease,[70] such as cancer,[71] surgery,[72] immobilisation (proxy marker: a hospital stay), hospital admission[73] and the initiation of hormone therapy.[74] Furthermore, we will adjust for the Charlson Comorbidity Index, which includes diabetes.[75–78] However, obesity, black ethnicity[79] and a family history of thromboembolic disease are not documented in the SNDS database, and so we cannot

rule out residual confounding in analysis 1 (the nested case–control study). In analysis 2 (the case-only design), cases serve as their own controls, which can mitigate the potential confounding factors (such as diet, smoking, the level of physical activity and a family history of thromboembolic disease) not documented in healthcare databases.[45 80]

Our study has several potential strengths, including the exhaustive nationwide coverage of the French population (thereby enabling an assessment of rare events and providing potentially greater statistical power), the theoretical absence of selection bias, given our use of the SNDS database, the quality of the recorded data (enabling estimation of the time of occurrence of VTEs), the implementation of two complementary methodological approaches and the definitions of outcomes that encompass VTEs managed in outpatient and inpatient settings.

The study's potential limitations include the difficulty of tracking all VTEs (the use of an algorithm for the identification of inpatient and outpatient diagnoses of VTE in the health insurance database is, however, currently being validated); potential information bias on hormone therapy, since a proportion of these treatments are not reimbursed and therefore cannot be detected in the SNDS; a potential lack of statistical power; and the inability to take account of some risk factors for VTEs (including obesity and a family history of thromboembolic disease) in the case–control design, although we believe that these potential confounding factors should affect cases and controls to the same extent.

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Acknowledgements We thank David Fraser for the English language revision and Stéphanie Mehrand, the Director of the French Eczema Association for her contribution to this work.

Contributors PB and CD wrote the first draft of the manuscript. PB, L-MS, AL, DS, GC, PG, AD, EO and CD conceived the scoping review and developed the research questions and the search strategy. All authors critically reviewed drafts and edited the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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